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Screening of Antidepressant Activity of Ethanolic Extract of Carica papaya L. Leaves in Rats

Sindhu L*, Dr.Nataraj GR, Sumith.S, Imtiyaaz NR
Department of pharmacology, SJM college of pharmacy, Chitradurga-577502

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ABSTRACT

Background: In recent decades, traditional plant-based treatments for depression have gained significant attention. Studies have shown that various parts of the Carica papaya plant, such as seeds, roots, bark, and fruit, have potential antidepressant effects in both animals and humans.

Aim & Objectives: To examine the protective role of ethanolic Carica papaya leaf extract in Chronic Unpredictable Stress (CUS)-induced depression in Wistar albino rats and explore its antidepressant effects.

Methods: The study spanned a 14-day period, utilizing a Chronic Unpredictable Stress (CUS) induced rat model. On the 15th day, behavioral assessments were conducted using a Rota rod, Actophotometer, and elevated plus maze. Biochemical parameters including Lipid peroxidation (MDA) and Catalase were also measured. Thirty rats were distributed into five groups, comprising a naïve control, positive control, standard (Imipramine 10mg/kg), and two distinct doses of EECP (250 & 500mg/kg) combined with CUS. Data analysis was performed using One-way ANOVA followed by Tukey's multiple comparison test.

Results:EECP treatment yielded increased locomotor activity, enhanced motor coordination, and a reduction in Depressive-like behavior compared to the positive control group. Furthermore, EECP administration (250 & 500mg/kg) exhibited a significant dose-dependent increase in Catalase levels and a reduction in MDA levels when compared to the stress control group.

Conclusion: The study concludes that the ethanolic extract of carica papaya L. leaves demonstrates a substantial antidepressant effect within a CUS-induced behavioral model.

Keywords: Carica papaya L., antidepressant activity, Ethanolic extract, chronic unpredictable stress.

I. INTRODUCTION

The globally burden of disease is significantly impacted by depression, a prevalent and destroying psychiatric ailment. There are 322 million people suffering from depression globally, according to the World Health Organization.[1]Depression is brought on by chemical imbalances in the brain that may be hereditary, demanding life changes, stroke, Parkinson's disease, social isolation, cancer etc.[2]

Depressive disease can result from serotonergic and neuroendocrine dysfunctions in response to persistent stress. According to clinical investigations, the hypothalamic-pituitary-adrenalaxis hyperactivity can increase cortisol levels by encouraging the over secretion of corticotrophin releasing factor.[3] There are various synthetic drugs are available for the treatment of depression are SSRI (Selective serotonin reuptake inhibitors)- Fluoxetine, Fluvoxamine, Sertraline, Paroxetine, TCA (Tricyclic antidepressants)- Imipramine, Amitriptyline, Clomipramine, MAOIs (Monoamine oxidase inhibitors)- Selegiline, However, despite their ability to treat patients, these medications have a number of side effects, including erectile dysfunction, nausea, sleeplessness, mania, tremor, hypertensionetc.[4]

Carica papaya Linn is one of the valuable plants utilized for a variety of medical applications. Leaves, fruit and seeds of are used as ethno medicine. To treat asthma, leaves are smoked and inhaled instead of tobacco. It has many activities, according to earlier scientific studies. When given as a decoction, it normalises the pulse rate in cases of fever and has diuretic properties.[5]

In several Asian countries, fresh C. papaya leaves are used in place of spinach. Patients with dengue fever are given C. papaya leaf juice as an immunity booster because it boosts white blood cell counts and detoxifies important organs. The leaf juice is also known to work as an anticancer agent and boost the key signalling molecules levels, i.e., activation of Th1 type cytokines and the immune system. The C. papaya leaves are an

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excellent source for antioxidants, minerals, and alkaloids. The carpaine is believed to reduce blood pressure, relax uterine muscles, and act as calcium antagonistic agent.[6]

Current allopathic treatment for depression is associated with side effects and adverse effects. So, there is a need to explore more herbal sources which can resolve the problem of depression. Therefore, in consideration of the above facts, the present study aimed to evaluate the antidepressant potential of ethanolic extract of Carica papaya L. leaves by using animal models.

II. MATERIALS AND METHODS

Collection and Authentication of plant:

Carica papaya L. leaves were collected from local garden in Chitradurga, Karnataka. The fresh leaves were subjected for observation for removal of damaged leaves & dried under shade. The dried Leaves were subjected to size reduction by electric grinder. The leaves material was identified and authenticated by botanist Niveditha B TAssistantProfessor, Jyanagangothri PG Centre, GR Halli, Davanagere University, Chitradurga. Karnataka, 577502.

Preparation of Plant Extract:[7]

- Carica papaya L. leaves were collected,cleaned, shade dried at room temperature and pulverised.
- The powder of leaves of Carica papaya L Leaves. was packed in Soxhlet apparatus and extracted with ethanol (95% v/v) at 40°C.
- The extract underwent filtration using Whatman No.1 filter paper, followed by concentration under reduced pressure, and was subsequently stored in an airtight container for future use.
- The percentage yield of the corresponding extract was calculated.

Experimental Animals:

Animal ethical clearance was obtained from Institution Animal Ethics Committee (IAEC) for experimental purpose **(Ref No: SJMCP/IAEC-03/August-2022)**. Healthy Adult Wistar Albino rats weighing about 150-200g of either sex were used for this study. The animals were obtained from Biogen Laboratory Animal Facility, Bangalore – 562107.

Preliminary phytochemical screening:[8,9]

Preliminary phytochemical investigations were carried out on test extract for the detection of phytoconstituentby following literature reported methods.

Selection of screening Dose:[10]

The selection of antidepressant activity dosage was determined in accordance with previous acute toxicity studies of ethanolic extract from Carica papaya L. leaves conducted by Yamte L. R. et al., where the following dosages were adopted:
- Low dose: 250mg/kg.
- High dose: 500mg/kg.

Experimental design:[11]

The animals were divided into five groups with six rats each: (n=6).

Table 1: Experimental design

Group 1	Negative control	Standard diet, water ad libitum.
Group 2	Positive control	Normal saline (10ml/kg, p.o.) + CUS for 14 days.
Group 3	Standard group	Imipramine (10mg/kg, p.o.) + CUS for 14 days.
Group 4	Test group 1	Carica papaya L. leaves extract Low dose of 250mg/kg b.w (p.o.) + CUS for 14 days.
Group 5	Test group 2	Carica papaya L. leaves extract High dose of 500mg/kg b.w (p.o.) + CUS for 14 days.

CUS- chronic unpredictable stress.

Induction of chronic unpredictable stress (CUS):[12]

- Animals were grouped and divided into five groups each consisting of six rats.
- Animals were treated according to grouping as mentioned above i.e., normal saline, standard drug and extract of Carica papaya L. Leaves for group 1, 2, 3, 4 and 5 respectively.
- The treatment was given daily for 14 days 1hr. before exposure to stressorrandomly,each dayat different times of day during screening period.Negative control rats were left

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undisturbed while, other groups of animals were subjected to CUS.

- Rats was submitted to the Behavioral tests 24 h after the last stressor.

Table 2: Various types of stressors and its duration.

Sl. No	Stressor	Duration
1.	Cold Swim (50^{O}C)	10 min
2.	Food and water deprivation	16h
3.	Smell stimuli (Acetic acid)	16h
4.	Electrical stimuli(0.7 mA, 3 s/min)	3 min
5.	Wet wood	16h

1. Elevated plus maze:[13]

Elevated plus maze is a commonly used behavioural model to determine antidepressant activity. Elevated plus maze test was performed according to Handley and Mithani. Elevated plus maze consists of 4 arms (2 open arms and 2 closed arms) attached at a junction (central platform). The plus maze was elevated to a height of 50cm above ground level. Animals of each group control, standard, and test were treated with normal saline, standard drug (Imipramine 10 mg/kg), and test extracts of EECP at 250mg/kg and 500mg/kg respectively one hour before the exposure to CUS and followed by cognitive behavioural assessment after 30 mins of CUS. Rats were placed at the junction of four arms, facing toward an open arm. The number of entries, time spent in each arm and centre was recorded for 5mins. Increase in open-arm activity reflects anti-depressant behaviour. The apparatus was cleaned with alcohol in between the trials. Precautions taken to maintain noise free environment.

2. Rota rod model:[14]

Effect of motor coordination was assessed using rota rod model. Rota rod consists of a base platform and anon-slippery surface rotating rod of 3cm diameter and divided into five equal sections. The animals were pre-selected in a training session based on ability to remain on rod (at 12 rpm) for 2mins.Animals of each group control, standard, and test were treated with normal saline, standard drug (Imipramine 10 mg/kg), and test extracts of EECP at 250mg/kg and 500mg/kg respectivelyone hour before the exposure to CUS and followed by assessing motor coordination after 30 mins of CUS. Animals were placed on rod at a speed of 20 rpm over a period of 30, 60, and 90mins. Falling off time was automatically recorded. Time spent in the apparatus was observed for 5min duration (300s). The apparatus was cleaned thoroughly with alcohol in between trials

3. Locomotor activity by Actophotometer.[15]

Locomotor activity of Wistar Albino Rats using Digital Actophotometer. The Actophotometer comprises a square field which measures about 35×35 cm with walls on all four sides that are fixed with photocells. Before the start of the experiment, the photocells were tested thoroughly. The total count of beam crossings made by each individual animal was automatically computed during a 5-minute period.Animals of each group control, standard, and test were treated with normal saline, standard drug (Imipramine 10 mg/kg), and test extracts of EECP at 250mg/kg and 500mg/kg respectivelyone hour before the exposure to CUS and followed by assessing locomotor activity after 30 mins of CUS.

Biochemical assessment of brain homogenate includes the following:

1. Catalase assay:[16]

Catalase activity within the brain homogenate was determined through a continuous spectrophotometric rate assessment, utilizing the Beers and Sizer method to evaluate antioxidant status. To the supernatant, a 2.5ml portion of phosphate buffer (pH 7.8) was added and then incubated at 25°C for a duration of 30 minutes. Following the transfer of the mixture into a cuvette, absorbance was spectrophotometrically measured at 240 nm. Subsequently, hydrogen peroxide was introduced, and the variation in absorbance was tracked over a 3-minute interval. The recorded value is expressed as µmol of H2O2/min/mg of wet tissue.

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Calculation:

$$\text{Cat (U)}/100\ \mu\text{l of sample} = \frac{dy}{dx} \times \frac{0.003}{38.3956 \times 10 - 6}$$

Where,
dy/dx=Changeinabsorbance
38.3956×10^{-6}=Molar extinctionco-efficientofH_2O_2at 240nm

2. Lipid peroxidation: [17]

Malondialdehyde (MDA) levels were assessed following Satoh's method. Initially, 75 mg TBA was dissolved in 15% TCA with the addition of 2.08 ml of 0.2 N HCl to reach a final volume of 100 ml. Then, 3.0 ml of this reagent was mixed with 0.75 ml brain homogenate. The test tubes were boiled for 15 min, cooled, and centrifuged for 10 min at 10,000 rpm. Supernatant absorbance was read at 535 nm against a blank, and results were expressed as mol/mg of protein.

Calculation:

$$\text{Conc. of MDA} = \frac{\text{Abs } 532 \times 100 \times \text{VT}}{(1.56 \times 105) \times \text{WT} \times \text{VU}}$$

Where,
Abs_{532}isabsorbance
$V_T$is total volume of mixture (4ml)
$1.56\times10^5$is molar extinction co-efficient
$W_T$isweightofdissectedbrain
$V_U$isaliquotvolume(1ml)

III. STATISTICAL ANALYSIS:

The data obtained from the above findings was subjected to statistical analysis using one-way ANOVA followed by Tukey's Kramer Multiple Comparison Test to assess the statistical significance of the result.

IV. RESULTS:

Percentage yield of ethanolic extract:**13.14%**
Colour and consistency: Dark green andsticky consistency.

Preliminary phytochemical screening:

Preliminary phytochemical screening of EECPleaves confirms the presence of carbohydrates,Proteins &aminoacid, alkaloids, glycosides, flavonoids, tannins, steroids, and phenolic compounds.

Antidepressant activity:

A test sample of Carica papaya L. leaves was screened for antidepressant potential by employing the behavioural and biochemical test in Wistar albino rats of either sex weighing 150-200g.

1. Elevated plus maze model:

The ethanolic extract of Carica papaya L. leaveswas screened forantidepressant activity in an elevated plus maze using CUS induced rat model. parameters studied in this model were a number of entries and time spent by the rat in open arm and center and closed arm. Assessment of cognitive behaviour was done. In the EPM model, Positivecontrol group animal permanence to open arm and center and closed arm was compared to the standard group (Imipramine 10mg/kg), low dose(250mg/kg), and high dose of EECP (500mg/kg). TheStandard group (Imipramine 10mg/kg) showed an extremelysignificant (***P<0.001) increase in both the number of entries and time spent in the open armcompared to the positive control group, suggesting antidepressant activity.In contrast, administration of EECP at low dose (250mg/kg) & high dose (500mg/kg) had shown a less significant (*P<0.05, and ^{ns}P>0.05) in the number of entries compare to positive control group. However, both the doses of EECP-treated rats exhibited anextremely significant (***P<0.001) increase in the time spent in the open arm compared to the positive control group.

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Table 3: Effect of EECP leaves in Elevated Plus Maze model

Sl no	Treatment	Number of entries (counts/5min)			Time spent (sec) in 5mins		
		Open arm	Closed arm	Center	Open arm	Closed arm	Center
I	Negative Control	8.66 ± 0.88	11.33 ± 0.88	6.66 ± 0.88	31.67 ± 6.27^{ns}	155.2 ± 13.2	42.5 ± 12.48^{ns}
II	Positive Control	3.5 ± 0.76	16.83 ± 0.70	4.5 ± 0.73	19.83 ± 3.38	246 ± 11.72	34.5 ± 9.72
III	Standard Group	10.5 ± 0.93^{***}	5.5 ± 0.72^{***}	8.5 ± 0.76^{**}	111.8 ± 16.1^{***}	133 ± 17^{***}	51.83 ± 10.31^{ns}
IV	Low Dose of EECP (250mg/kg)	5.83 ± 1.249	4.00 ± 0.683 ***	2.16 ± 0.477	121 ± 12.307 ***	119.5 ± 13.50^{***}	61.16 ± 13.96^{ns}
V	High Dose of EECP (500mg/kg)	7.33 ± 0.802	3.166 ± 0.477^{***}	1.5 ± 0.428	127.33 ± 4.75^{***}	108.66 ± 8.08^{***}	63.16 ± 6.978^{ns}

Values were expressed as Mean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01 and *P < 0.05 and ^{ns}P > 0.05. positive control group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison tests).

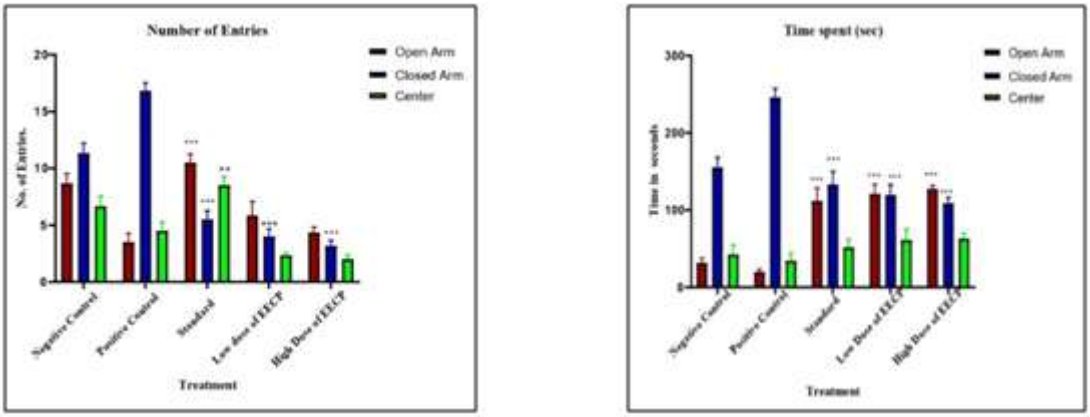

Figure 1: Effect of EECP leaves in Elevated Plus Maze model

2. Rota rod model:

Muscle grip strength was assessed using a rota-rod apparatus, with mean fall-off time as the measure of muscular rigidity. The positive control group exhibited reduced fall-off time, indicating muscle incoordination. However, the standard group (Imipramine 10mg/kg) produced an extremely significant (***P<0.001) increase in the fall off timewhen compared to the other groups in all time intervals (30mins, 60mins, 90 mins). Administration of EECP at low dose (250mg/kg) had shown moderately significance (**P<0.01) and EECP at high dose (500mg/kg) had shown a highly significance (***P<0.001) at 30mins, 60mins, 90 mins it had shown animals-maintained equilibrium and stayed on rotating rod for long period without falling compared to positive control group.

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Sl. No	Treatment	Fallof time(sec)
I	Negative Control group	171±11.39
II	Positive controlgroup	80±2.93^{ns}
III	Standard group (Imipramine) 10mg/kg	153.8±8.36***
IV	LowdoseofEECP(250mg/kg)	112.33±6.44**
V	High dose of EECP (500mg/kg)	132.66±4.12***

Table 4: Effect of EECP leaves in Rota-rod model.

Valueswere expressed asMean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01 and ^{ns}P > 0.05. positivecontrol group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison tests).

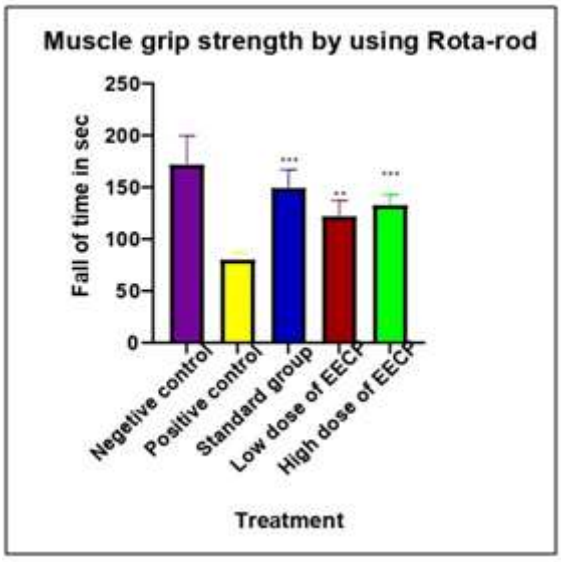

Figure 2: Effect of EECP Rota-rod model

3. Locomotor activity by Actophotometer.

All the animals were evaluated for locomotor activity using an Actophotometer. In this model, the ambulatory score was recorded based on their ability to cross a beam of light in the apparatus. The Imipramine-treated group (10 mg/kg) and the EECP-treated groups (250 mg/kg & 500 mg/kg) showed an increase in locomotor activity compared to the positive control group. It was observed that locomotor activity progressively increased over the entire 5 minutes in all drug-treated groups.The Standard group (Imipramine 10mg/kg) showed anextremely significant (***P < 0.001) increase in locomotor activity. In a low dose of EECP (250mg/kg)&high dose of EECP (500mg/kg), the treated group had shown moderatelysignificant (**P<0.01) compared to positive control group.

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Sl.No	Treatment	AmbulatoryScores
I	Negative control	144.5±5.35
II	Positive control	76.50 ± 5.68
III	Standard Imipramine(10mg/Kg)	132.5± 6.04***
IV	Low dose of EECP (250 mg/Kg)	112.33±6.484**
V	High dose of EECP (500mg/Kg)	132.6±4.12**

Table 5: Effect of EECP leaves in Actophotometer

Values were expressed as Mean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01, *P < 0.05 and nsP> 0.05. positive Control group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison tests).

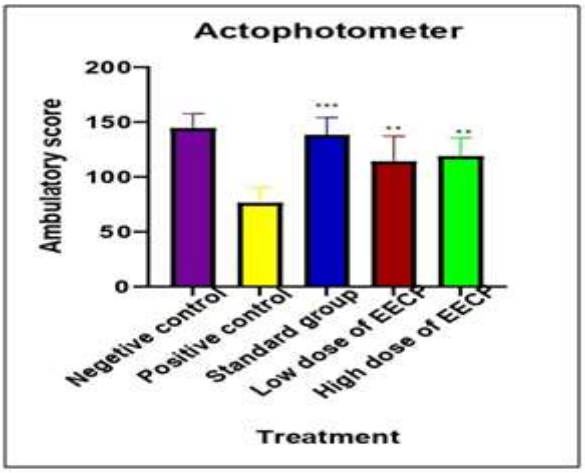

Figure 3: Effect of EECP leaves in Actophotometer model

Biochemical assessment of brain homogenate:

1. EffectofEECPonCatalaseassay

The breakdown of hydrogen peroxide indicates the level of catalase present in brainhomogenate which was done by using endogenous anti-oxidant catalase assay. The data revealed that, anextremely significant elevation in CAT level was seen in standard Imipramine, low dose and high dose of EECP (250 mg/kg & 500 mg/kg)with(***P< 0.001), (***P< 0.001) and (***P < 0.001) respectively when compared topositive control group. The effect of EECP on catalase assay is given in Table No:6 &FigNo:4.

Table 6: Effect of EECP on Catalase assay

Sl.No	Treatment	Catalase(µmol/min/mgprotein)
I	Negative control	26.182±0.508
II	Positive control	17.267±0.419
III	Standard Imipramine(10mg/Kg)	37.941± 0.394***
IV	Low dose of EECP(250mg/Kg)	35.332±1.082***
V	High dose of EECP (500mg/Kg)	35.332 ±1.082***

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Values were expressed as Mean±SEM(n=6);Significance values are:*P<0.05,**P<0.01 and***P< 0.001. positive control groups all groups.

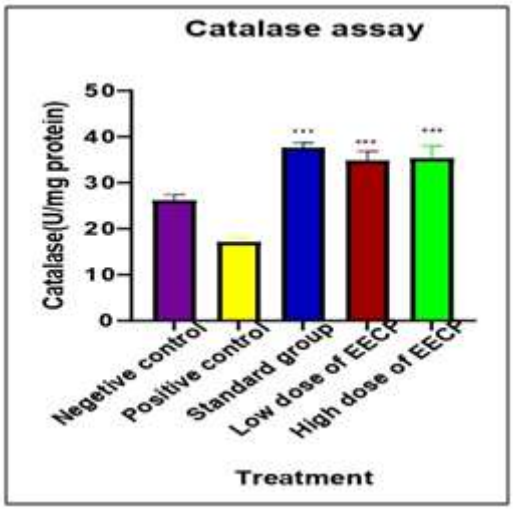

Figure 3: Effect of EECP on catalase assay

2. Effect of EECP on Lipid peroxidation:

Malondialdehyde (MDA) is a reliable indicator of peroxidation. Increase in free radicalcauses over production of MDA this was determined by reactive brain homogenatesample with Thiobarbituric acid (TBA) in lipid peroxidation assay. The data revealedthat, the standard Imipramine (10mg/kg), low dose and high dose of EECP (250 mg/kg &500mg/kg) showed significant reduction in the level of MDA when compared to positive controlgroup. The effect of EECP on lipid peroxidation assay is showed in Table No: 7&FigNo:5

Table 7: Effect of EECP on LPO assay

Sl. No	Treatment	MDA (µmol /mg protein)
I	Negative control	2.243±0.048
II	Positive control	3.494±0.035
III	Standard Imipramine(10mg/Kg)	2.345± 0.036***
IV	Low dose of EECP (250mg/Kg)	2.446±0.024***
V	High dose of EECP (500mg/Kg)	2.288 ±0.094***

Values were expressed as Mean±SEM(n=6);Significancevaluesare:*P<0.05,**P<0.01 and***P< 0. 001.positive controlgroupvsallgroups.

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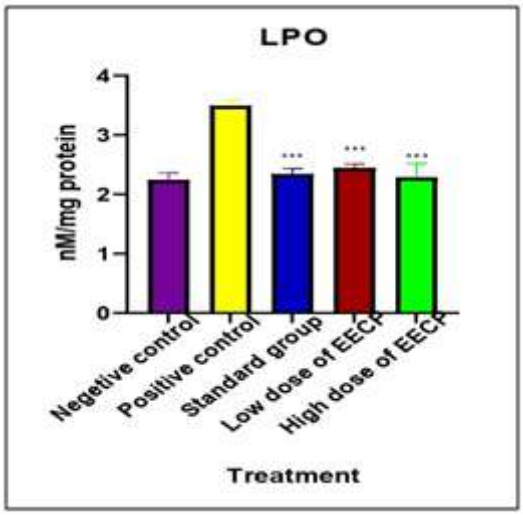

Figure 4: Effect of EECP on Lipid Peroxidation

V. DISCUSSION:

Depression is a prevalent psychiatric disorder characterized by a decline in psychosocial functioning. It constitutes a significant public health challenge due to its substantial morbidity and mortality rates, as well as its association with increased risk of comorbid conditions. One prominent theory explaining the development of depression is the monoamine hypothesis, which postulates that there is a reduction in the activity of certain biological amines such as serotonin (5-HT), noradrenaline, and dopamine in individuals experiencing depression. It is widely acknowledged that the serotonin system plays a crucial role in the neural regulation of mood, and augmenting 5-HT neurotransmission serves as the foundation for the therapeutic efficacy of various classes of antidepressant medications.[18]

An effort has been made to establish the scientific validity to explore the antidepressant effects of Carica papaya leaves based on literature and traditional applications. To determine the existence of several kinds of secondary metabolites that are in charge of providing pharmacological activity, phytochemical studies were carried out. The results of the phytochemical analysis of Carica papaya leaves showed that the ethanolic extract contained flavonoids, tannins, alkaloids, glycosides, phenols, and amino acids.[19]

The present antidepressant activity EECP in rats, revealed increase the number of entries into the open arm and spent more time exploring the open arms (measured by Elevated plus maze), improved motor coordination (measured by Rotarod apparatus), increased locomotor activity (measured by Actophotometer). The EECP also significantly increased catalase activity & reduced the lipid peroxidation level in brain, which shows that their antioxidant effects are mediated by reductions in oxidative stress. The remarkable resemblance in results is in harmony with the discoveries made by Dayalan Get al. (2022) and Hussain Het al. (2022), who arrived at a similar inference that their individual compounds showcase antidepressant activity.[20,21]This suggests that EECP may alleviate depression by enhancing antioxidant defences and reducing oxidative stress in the brain.

It has been discovered that the leaves of the carica papaya are efficient against a variety of pharmacological actions because they are rich in flavonoids, phenols, and tannins, among other compounds. The Significant antidepressant efficacy was seen in albino rats treated with an ethanolic extract of carica papayaleaves. Although the antidepressant efficacy of carica papaya leaves was validated in the current study, more research is needed to understand how it works. Thus, there would be several opportunities for researchers in the future.

VI. CONCLUSION:

The study found that the EECP leaves showed significant potential against chronic stress-induced depression in rats. Using various Behavioral and oxidative stress assessment models, the leaf extract demonstrated effectiveness in reducing depression, enhancing muscle grip strength, and increasing locomotor activity and increased catalase activity and reduced lipid peroxidation in rat brain. This suggests the extract has notable antidepressant properties, likely due to

compounds like flavonoids, tannins, steroids. However, further research is needed to isolate active constituents and understand the exact mechanisms involved, enhancing its potential as a depression treatment.

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